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EFFECTS OF COMBINED CAFFEINE AND EPHEDRINE INGESTED WITH A LIQUID MEAL ON SUBSEQUENT EXERCISE PERFORMANCE

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EXECUTIVE SUMMARY

The ability to maintain or enhance our soldiers' performance could be crucial to a mission in scenarios such as extended search and rescue and sustained operation. In this regard, DCIEM has been investigating the effects of ingesting various drugs to determine their effect on physical performance. Two such drugs, Caffeine (C) and ephedrine (E) ingested in combination have been shown to enhance physical performance. However, in some subjects, the combination has caused nausea and vomiting during high intensity exercise. These subjects had fasted for 10-12 hours. It was speculated that this fasting may have predisposed the subjects to developing nausea. Therefore, this study evaluated the effects of ingesting a standardized liquid meal, i.e., a can of ENSURE PLUS®, after drug ingestion and one hour before exercise, to see if the incidence of nausea could be reduced. The results indicated that in those subjects that had ingested the meal, it did not alleviate the problem of nausea, and further it attenuated the effect of the drug on performance. This response may have been a result of a number of factors, i.e., unfamiliarity of meal, closeness of meal ingestion to time of exercise, and length of fasting. Before the Canadian Forces can use these drugs to enhance physical work more studies are needed to investigate whether or not a more familiar light meal, e.g., juice, toast, muffin, given 1.5 to 2 hours before exercise would be more effective in reducing the incidence of nausea associated with drug ingestion.

ABSTRACT

The combination of caffeine (C), and ephedrine (E) has been reported to have an ergogenic effect on high intensity aerobic exercise performance (Bell et al., 1995). A serious problem encountered with this treatment is that 25% of the subjects experienced vomiting and nausea while engaging in hard exercise after the treatment. The present study was undertaken to investigate whether food ingestion would alleviate the problem and to see if the ergogenic effect of the drugs on aerobic performance could be maintained. Thirteen healthy untrained subjects, 6 males and 7 females, completed 2 randomized and double blind, cycle ergometer trials to exhaustion at a power output equivalent to ~85% $\dot{V}O_2$peak 1.5 hours after ingesting C (5 $mg \cdot kg^{-1}$) and E (1 $mg \cdot kg^{-1}$), or a placebo (P). The meal, a can of ENSURE PLUS®, was given to the subject to drink 30 minutes after drug or placebo ingestion. Each trial was separated by one week. Venous blood samples were obtained and analyzed for caffeine and ephedrine levels pre- and 1.5 hours post-drug ingestion. $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, and RQ were measured every minute throughout the exhaustion ride. Heart rate was also monitored during the exercise session and the final heart rate recorded. Blood drug levels (mean ± SD) of caffeine and ephedrine immediately before the exhaustion ride were 51.9 μM (± 21.4) and 0.434 μM (± 0.127). The ingestion of the liquid meal did not reduce the incidence of nausea caused by the drugs during exercise; in fact, the meal tended to produce greater intestinal distress. After the trials it was discovered that only one of the seven females consumed all of the liquid meal. This may explain some of the differences between the male and female data. The times to exhaustion for the drug trials were significantly longer than the placebo times for the females (19.6 ± 3.0 vs 14.7 ± 4.9) but not for the males (9.8 ± 3.3 vs 10.4 ± 3.0). The drugs did not affect $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$ or RQ. Final heart rates were significantly higher for the drug trials. In conclusion, the food ingested, i.e., ENSURE PLUS®, was not effective in reducing the previously observed high incidence of vomiting and nausea. The reasons for the ineffectiveness of the liquid meal was attributed to it's unfamiliarity and unpalatability to the subjects, and the length of time ingested before exercise. Furthermore, the ergogenic effect of the drugs was not noted in those subjects that ingested the meal.

Key words: ergogenic aids, caffeine, ephedrine, performance, food, $\dot{V}O_2$peak

INTRODUCTION

It was reported that there was an ergogenic effect on endurance performance in fasted subjects following ingestion of caffeine (C) combined with ephedrine (E) (Bell and Jacobs, 1995; Bell et al., 1996). There was, however, an unusually high incidence of vomiting, experienced by 25% of the subjects during exercise after C+E treatment. These subjects did not demonstrate an ergogenic effect of the C+E. Prior to these experiments all subjects had been fasting for 10-12 hours. It was thought that this fasting may have predisposed some of the subjects to developing nausea. Furthermore, it was speculated that if the subjects were allowed to take food after their drug ingestion then perhaps the incidence of vomiting might be reduced.

Thus the purpose of this experiment was to evaluate the effects of ingesting a standardised liquid meal, 30 minutes after C+E ingestion on the incidence of emesis and/or nausea during subsequent exercise, and to determine if the ergogenic effect of C+E was maintained when a liquid meal followed the drug ingestion.

METHODS

Subjects

Informed consent was obtained from 13 subjects (6 males and 7 females), with a mean age of 28 years (± 7), weight of 68.7 kg (± 8.1), height of 1.73 m (± 0.07), and $\dot{V}O_2$peak of 43.0 $mL \cdot kg^{-1} \cdot min^{-1}$ (± 6.3). The subjects were not trained competitive athletes. Participation was further restricted to individuals who had been consuming the equivalent of at least 7 cups of caffeinated coffee per week.

Procedures

A pilot study was run to determine the approximate time of peak plasma concentration of caffeine and ephedrine after ingesting a can of ENSURE PLUS® which is a mixed nutrient drink. The C+E combination was first ingested and then 0.5 h later the ENSURE PLUS® was consumed. From the pilot data, exercise start time was set at 1.5 h post drug ingestion.

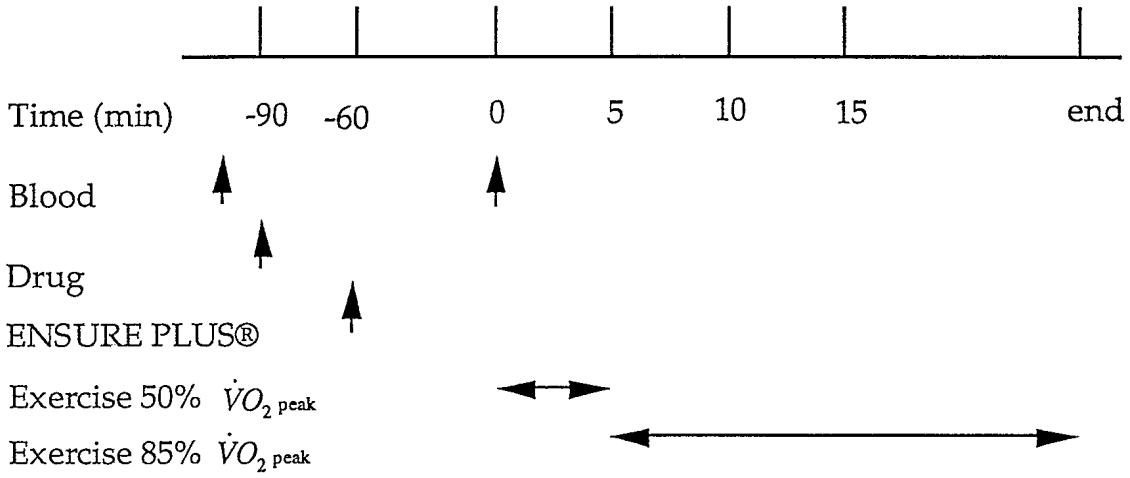
During the study, the subjects visited the laboratory on five separate occasions. On visit one, subjects were medically screened and then had their $\dot{V}O_2$peak determinted on an electrically braked cycle ergometer (Ergomed 920/930, Siemems-Elema, Sweden) by a four (4) minute stepwise incremental

protocol. Male subjects began pedaling at a power output of 75 watts (W) and this was increased 50 W every four minutes until exhaustion. Females started at 60 W and this was increased by 30 W every four minutes until exhaustion. The relationship between oxygen uptake and power output was derived from this test. During visit two, the subjects were familiarised with the exercise test that was to be used during the experimental drug trials, i.e., the exhaustion ride (ER). This consisted of exercising for five minutes on an electrically-braked cycle ergometer with the load set at a power output equivalent to approximately 50% $\dot{V}O_2$peak and a pedal frequency between 60-100 revolutions per minute. This was followed by a ride to exhaustion at a power output of approximately 85% $\dot{V}O_2$peak at the same pedaling frequency. The ride ceased when the subject's pedal frequency dropped below 50 revolutions per minute. During visit 3 - the control trial - the subjects were familiarized with the blood sampling procedures. A blood sample was taken just prior to exercise and then the subject again performed the ER. Visits 4 and 5 were the treatment trials. These were separated by a minimum of one week. The treatments were randomized and double blind. The subjects reported to the laboratory in a fasted (12 hours) and rested state. A blood sample was taken 1-2 minutes before capsule ingestion. One half hour after capsule ingestion the liquid meal was given to the subject to drink. The subject then waited another hour, a second blood sample was taken and then the ER protocol commenced. Ten mL of blood were drawn at each sample. Following the ER, the subjects were ask if any feelings of nausea occurred during the trial. Vomiting was self evident and noted. A time line of events for the treatment trials is shown below (Figure 1).

Drug and Placebo Administration

All treatments were ingested in opaque gelatin capsules. The subjects consumed 5 $mg \cdot kg^{-1}$ body weight of C plus 1 $mg \cdot kg^{-1}$ body weight E, or a placebo 90 minutes before exercise. The placebo consisted of the same number of capsules, but contained Metamucil®, a dietary fiber. The order of treatments was randomised among subjects.

Figure 1: Time Line of Events for Treatment Trials



Measurements

Volume of oxygen consumption ($\dot{V}O_2$), volume of carbon dioxide production ($\dot{V}CO_2$), and volume of ventilation ($\dot{V}_E$) were analyzed every minute via a metabolic cart (Ametek, model OCM-2, USA) during the measurement of $\dot{V}O_2$peak and during the ER. Heart rate was monitored during all exercise sessions (Polar, model Vantage XL, USA). Plasma blood samples were assayed for both C and E by gas chromatograph-mass spectrometry electron impact single ion monitoring (Hewlett Packard, model MSD 5970a, USA).

Meal Ingestion

After the trial was completed, it was discovered that a number of the females (5 of 7) did not adhere to the protocol, i.e., they did not ingest the can of ENSURE PLUS®. When asked why they did not ingest the product they responded they did not like its texture or taste. All males drank the product regardless of the taste or texture but a number of them did comment they did not like it.

Data Analyses

All the data, whether the subjects vomited or not during the trials, are included. Further, when it was found that the females did not follow the protocol and the males did, it was decided that the data of each gender should be analysed separately. A repeated measures analysis of variance was used to compare the dependent variables across treatments. When a post hoc comparison was required, a means comparison contrast technique was

employed (Gagnon et al., 1989). All statistical analyses were done using SuperAnova® software (Gagnon et al., 1989). For all statistical analyses the 0.05 level of significance was used.

RESULTS

Drug Trials

The levels of C and E in the plasma 90 minutes after ingestion were 51.9 μM (± 21.4) and 0.434 μM (± 0.127), respectively. Neither were detectable in the sample taken prior to ingestion (time - 90 minutes).

Nausea and Vomiting

Table 1 reports the incidence of nausea and vomiting that occurred.

Table 1. Incidence of Nausea and Vomiting

Nausea and Vomiting

	PLACEBO				C+E			
	Nausea		Vomit		Nausea		Vomit	
	yes	no	yes	no	yes	no	yes	no
Males								
1		x		x	x			x
2	x			x		x		x
3	x		x		x		x	
4	x			x	x			x
5		x		x	x		x	
6		x		x	x			x
subtotal	3	3	1	5	5	1	2	4
Females								
1	x			x	x			x
2		x		x		x		x
3		x		x		x		x
4	x		x		x		x	
5		x		x		x		x
6		x		x		x		x
7		x		x	x			x
subtotal	2	5	1	6	3	4	1	6
Total	5	8	2	11	8	5	3	10

Eight of 13, or 62%, of the subjects were nauseous when taking the drug and food combination, and 3 of the 13 vomited. Two males vomited during the ride, one female vomited after the ride when she was in the shower. Five (5) of the 13 or 38% reported being nauseous on the placebo food trial and 2 of these vomited. One vomited during the trial (male) which caused cessation of the ride, and the other (female) vomited after the ride was over. Four (4) of these same five reported being nauseous during both trials.

Endurance Ride

The females significantly prolonged their time to exhaustion after C+E treatment (19.6 ± 7.8 min) compared with both the placebo (14.7 ± 4.9 min) and control (14.9 ± 3.0 min) trials. In contrast, the males showed no increase in time to exhaustion after C+E (9.8 ± 3.3 min) compared with either placebo (10.4 ± 3.0 min) or control (11.1 ± 2.5 min) trials (Figure 2). The relative intensity of exercise during the endurance ride did not differ between genders.

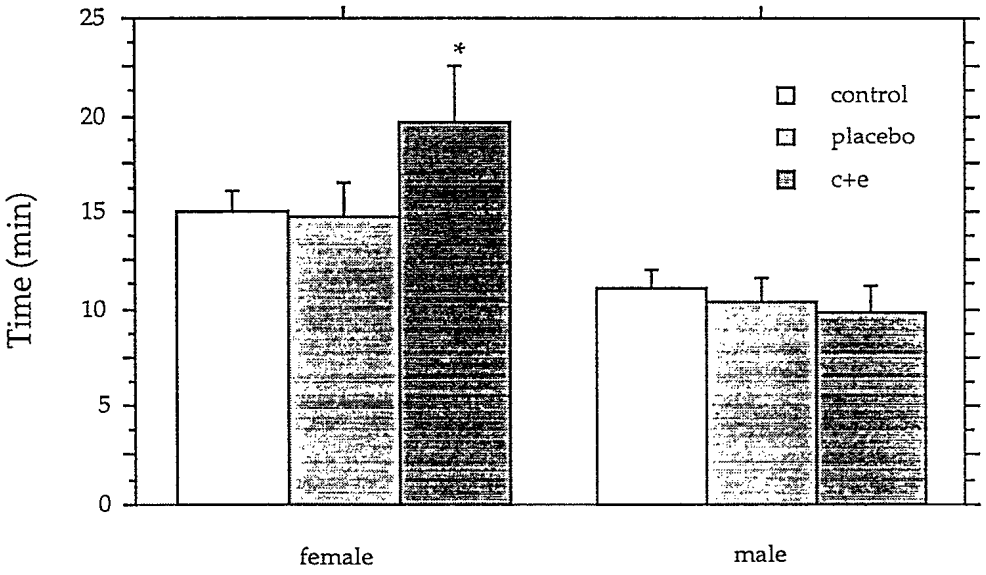


Figure 2. Time to exhaustion values are means ± SEM. * Significantly longer than other trials.

Respiratory Gas Exchange and Heart Rate

During ER, the C+E did not significantly affect $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$ or the repiratory quotient (RQ). The C+E treatment, however, produced a

significantly higher final heart rate (191 ± 12 beats•min^{-1}) compared to the placebo (184 ± 10 beats•min^{-1}) or control (186 ± 11 beats•min^{-1}) in all subjects.

DISCUSSION

Vomiting and Nausea

It was anticipated that the consumption of a liquid meal post drug ingestion might reduce the incidence of sickness observed in our earlier experiments with C+E (Bell and Jacobs, 1995; Bell et al. 1996). This speculation was not supported by the data for the males, who adhered to the protocol exactly. In this group, 2 out of 6 subjects vomited during exercise after ingesting the food and C+E. These results are similar to previous work where 4 of 12 subjects were sick when on the C+E and in a fasted state (Bell and Jacobs, 1995). In addition, in the present study, one of the males also vomited during the placebo run and 3 were nauseous. In the previous study (Bell and Jacobs, 1995), sickness and nausea were not evident during the placebo trial. Furthermore, none of the males in the present study or the previous study (Bell and Jacobs, 1995) vomited or were nauseous during the familiarisation trials when neither C+E nor ENSURE PLUS® was ingested. This suggest that ENSURE PLUS® may be adding to the distress, not alleviating it.

Care must be taken when interpreting the female data because most of the females did not ingest the liquid meal. Only one female vomited. This individual vomited during both the drug and placebo trials. She stated that she drank one half of the can of ENSURE PLUS® on her first trial which was her placebo run and that during her second trial she did not consume any of the liquid meal. In her case, it is evident that both the food and C+E caused the vomiting because she was not nauseous or sick during her familiarization trial. With regards to the other females, it was discovered that the only female who adhered to the drinking protocol was neither sick nor nauseous during her runs. She claimed to like the taste of the product. The other females ingested little of the product and the only positive outcome from these trials is that C+E ingestion appears to cause less nausea and sickness in females than in males. Still, however, 3 of 13 subjects who participated in this study were sick while on the drugs.

Why the others were sick when not on the drugs may be explained in a number of ways. First, the ENSURE PLUS® was a food supplement that was unfamiliar to most subjects. Most subjects did not like the taste of this

product. In fact, five of the seven females had difficulties ingesting it on the first visit, two did not take any and three did not consume the whole can. On the subsequent visit they consumed even less or none of the product. It may not be coincidence, therefore, that the females demonstrated a relatively large treatment effect of the C+E similar to previous findings when ENSURE PLUS® was not ingested (Bell and Jacobs, 1995).

Second, the fat content in the ENSURE PLUS® may have delayed gastric emptying (Hunt and Stubbs, 1975) and, thus, produced additional stomach distress during exercise. In addition, it is known that high intensity exercise and elevated catecholamine levels can impede gastric emptying (Murray, 1987; Costill and Saltin, 1974; Jenkinson and Morton, 1966; Hellebrandt and Tepper, 1934). In the present scenario, the administration of the drugs is known to increase resting catecholamine levels; this may lead to reduced splanchnic blood flow and an increased time for gastric emptying. Thus, the quantity of food in the stomach during the C+E trial may have been greater and produced a greater distress.

Third, the intervening duration after food ingestion and before exercise could also be critical. In the present study, only one hour intervened before heavy exercise. In other studies where 2 hours or more were given and ENSURE PLUS® was ingested (McLellan et al., 1995; Morris et al., 1996), there were no reports of sickness. In the study of McLellan et al. (1995), 75 trials were conducted without incidence of vomiting. Thus, it may be important to increase the waiting interval following the ingestion of ENSURE PLUS® prior to performing heavy exercise. A preferable strategy might be to ingest familiar food, wait a little longer, perhaps 2 hours, then commence exercise.

One final factor which may also be contributing to the problem has to deal with the length of fasting. The subjects came in from an overnight fast, i.e., lasting approximately 10-12 hours. They then had to ingest the drugs or the placebo. This was followed by the ENSURE PLUS® a half hour later and then 1 hour after the ENSURE PLUS® they commenced exercise. In the study by McLellan et al. (1995), subjects were fasted for four hours. They came to the laboratory, ingested the ENSURE PLUS® waited two hours, and then exercised at a similar intensity as in the present study. No sickness occurred in these subjects while in the present study two of thirteen became sick during the placebo runs.

In summary, a number of small factors probably accounted for the emesis and nausea. These include unfamiliar and unpalatable food, length of fasting, and, perhaps the most important factor, the length of time between eating and exercise.

Performance

The C+E produced a significant increase in time to exhaustion; specifically in the females. It was 33% longer than comparable placebo values. These are similar to previous results with males (Bell and Jacobs, 1995) and are the first data reported in female subjects. The males in this study, however, did not show an increased time to exhaustion, which is different from the previous study (Bell and Jacobs, 1995). The reason for this lack of improvement is believed to be related to the ingestion of ENSURE PLUS®, the short intervening interval after ingestion and the commencement of exercise, and the higher incidence of nausea and vomiting for the males compared with the females (see Table 1). Levels of C and E in the blood of the male and females subjects just prior to the ER were not different and the levels were similar to previously reported values (Bell and Jacobs, 1995). The lack of improvement in the males, therefore, can not be attributed to a lower blood drug concentration as a result of a higher food intake .

In conclusion, it was found that the liquid meal did not prevent the sickness associated with drug ingestion and high intensity exercise. Further, the ergogenic effect of C+E was blunted with the ingestion of the liquid meal when taken an hour before exercise. When the quantity of food ingested was reduced, i.e., in the female group, the C+E treatment yielded the previously demonstrated ergogenic effect.

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